

MINI-SYMPOSIUM

The development of cardiac rhythm

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The cardiovascular system is the first organ system to form and function in the developing embryo. In the early stages the heart is a slow conducting, single tubular structure generating an even peristaltic contraction. During embryogenesis it then develops into a four chambered heart with synchronous contraction for a dual circulation. These synchronous contractions of the atrial and ventricular chambers are dependent on the development of high conduction velocities resulting in alternating slow and fast conducting segments. In the early embryonic heart tube, an ECG similar to that of an adult has been recorded. This indicates the electrical activity of sequentially activated heart chambers,¹ so demonstrating the functioning of the cardiac conduction system (CCS), before any morphological development can be distinguished. Throughout the developmental process the heart must maintain its rhythmical contractions through coordinated activation of the myocardium.

The components of this system include the sinoatrial (SA) node, the atrioventricular (AV) node, and the ventricular conduction pathway consisting of the bundle of His, the right bundle branch, the left bundle branch, and the Purkinje fibres.

THE SINOATRIAL NODE

In the adult the SA node is found at the junction of the right common cardinal vein and the wall of the right atrium, within the terminal groove. These cells have the most rapid inherent rhythm so setting the rate for the rest of the myocardium, and thereby functioning as the dominant pacemaker. This pacemaker activity has been illustrated in chick embryos at an age approximately equivalent to 20 days in the human embryo.² The pacemaker activity develops in the inflow tract of the primary heart tube and is the first element to function in the CCS. Action potentials spread from the posterior inflow tract to the anterior outflow tract of the heart generating a wave of contraction.³ However, it is not until approximately 35 days of human development that a morphologically identifiable SA node can be seen.⁴ Little is known about mechanisms that initiate and maintain the growth of the SA node. The impulse is then conducted via the atrial myocardium to the AV node.

THE ATRIOVENTRICULAR NODE

When formed, the AV node is found at the base of the interatrial septum close to the endocardium, at the apex of the triangle of Koch. It delays the impulses passage from atria to ventricular myocardium. The AV node, like the SA node, performs this function before being morphologically identifiable,⁵ and is first recognisable when the looping heart divides into atrial and ventricular components from ~5 weeks of human development onwards.^{6–8}

THE ORIGIN OF NODAL CELLS

The nodal cells of the AV and SA node are similar to embryonic cardiomyocytes. They are small with a poorly developed sarcoplasmic reticulum and lack a functional contractile unit due to poorly organised actin and myosin

filaments. Advances in molecular markers have recently enabled us to trace the development of these nodes. In a murine model the GATA-6 reporter gene has marked an atrioventricular ring that subsequently integrates into the atrioventricular conduction system. This ring shows predominant staining in the wall to the right side of atrioventricular canal, thought to be the developing AV node during the process of chamber formation.⁷

VENTRICULAR CONDUCTION PATHWAY

The ventricular conduction pathway (VCP) enables the rapid passage of impulses into the contractile ventricular myocardium. This is facilitated by organised high conductance gap junction proteins. This is essential for activation of the ventricles from apex to base, resulting in the efficient ejection of blood from the ventricles into the outflow tracts at the base of the heart. It can be divided into sections. The bundle of His emanates from the AV node at the posterior right atrial wall near the atrial septum above the atrioventricular groove. This runs through the upper margin of the ventricular septum before bifurcating and becoming the left and right bundle branches which descend on either side of the septum. These end by dividing, to give rise to the Purkinje fibres. These fibres branch to form a terminal network that lies just underneath the cardiac endothelial surface.

ORIGIN OF THE CELLS OF THE VENTRICULAR CONDUCTION PATHWAY

Fate map studies using chick embryos have found that cells from three distinct embryonic origins—namely, the cardiogenic mesoderm, the neural crest, and the proepicardial organ—constitute the cell lineage of the heart. It had previously been suggested that the CCS originated from the neural crest. Indeed cells of the CCS do express markers common to neuronal cells such as HNK-1 and some neurofilament proteins.⁹ However, it has since been shown that the cells of the VCP are derived from a subset of embryonic myocytes. Retroviral lineage studies on chick embryo cells from each of the three cell lines were tagged using replication incompetent vectors.^{10–11} Tagged Purkinje fibre cells were found exclusively in the myocytes clones, and no conduction cells were produced from cardiac neural crest or primordial epicardial cells. These studies also went on to demonstrate that cells of the CCS were recruited locally rather than by “outgrowth” and branching of the early framework.

PURKINJE FIBRE DIFFERENTIATION

In the maturing chick embryonic heart Purkinje fibres develop in the subendocardium along coronary artery branches, suggesting a role for arteriogenesis in the differentiation of Purkinje cells.^{12–14} This led to the belief that embryonic myocytes may be induced to form Purkinje fibres by receiving paracrine signals originating from arterial

Abbreviations: AV, atrioventricular; CCS, cardiac conduction system; SA, sinoatrial; VCP, ventricular conduction pathway

vascular tissues. It has now been demonstrated that cultured embryonic myocytes convert to a Purkinje cell phenotype after exposure to one such paracrine factor, endothelin.¹⁵ Furthermore, this inductive response declined with the progression of development suggesting that the responsiveness of myocytes to endothelin is a distinct developmental process. The potent vasoconstrictor endothelin is a shear stress induced cytokine abundant in the arterial system, and endothelin receptors are present in all myocytes.¹⁶ This may be of particular importance in helping us to understand how the development of the CCS can be affected by environmental factors, such as shear stress or pressure. It should be noted that these studies used avian models. Optical mapping of cardiac electrical activity using a voltage sensitive dye in the murine CCS has demonstrated that a functional His-Purkinje system exists surprisingly early, even before septation has begun. Therefore, in the murine model a functioning network of conducting cells exists before the formation of the coronary vessels, so questioning the arteriogenesis theory.¹⁷ It may be that a basic structure is initially laid down following which cardiomyocytes continue to be recruited in order to expand the conductive cell network. This will require further lineage analysis studies.

DEVELOPMENTAL ARRHYTHMIA MECHANISMS

The abnormality of cardiac rhythm can be the consequence of a genetically determined ion pump dysfunction (that is, "channelopathies" such as Brugada and congenital long QT syndrome),^{18,19} or a developmental electrophysiology abnormality which can be either primary (such as nodal re-entry tachycardia and Wolf Parkinson White syndrome),²⁰ or secondary to congenital heart disease (for example, Ebstein's anomaly).²¹ Another possible developmental mechanism that has yet to be investigated in this field is the manifestation in adult life of diseases that have their roots in insults during early life, through the process of "programming".

CONCLUSION

While many aspects of cardiac development are now well understood, there has been a lag in our understanding of the development of the CCS. Recent advances in cellular and molecular processes are now helping us to uncover the mechanisms involved in the induction, patterning, and developmental integration of the CCS. At present this knowledge is based on studies using animal models which have helped us to gain insight into human development and disease. Further research is necessary in the hope that this will not only lead towards a better understanding of this area, but that it may also lead to the development of therapeutic applications such as the regeneration of damaged cardiac conduction tissue or the construction of biologically engineered cardiac conduction tissue.

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